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ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: BETA-BLOCKERS HAVING ANTIOXIDANT AND NITRIC OXIDE-DONOR ACTIVITY

(57) Abstract: Multifunctional beta-antagonist compounds are provided, that combine  $\beta$ -adrenergic receptor blocking activity with capability to scavenge superoxide and other reactive oxygen species, and that may further function as nitric oxide donors. The compounds are useful for preventing or treating disorders in which the treatment with  $\beta$ -antagonists is indicated, or which are associated with oxidative stress.

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## INTERNATIONAL SEARCH REPORT

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/385 A61K31/40 A61K31/4025 A61K31/403 A61K31/407  
 A61K31/433 A61K31/4436 A61K31/5377 C07D491/04 C07D493/04  
 C07D495/04 C07D498/04 C07D417/12 C07D417/04 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, BIOSIS, EMBASE, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/35961 A (UNIV BOSTON ;VITA JOSEPH A (US); WORCEL MANUEL (US); LOSCALZO JOSE) 25 May 2001 (2001-05-25) page 4, line 14 page 9, line 7 - line 13 page 9, line 31 - page 10, line 28 page 12, line 3 page 18, line 20 - page 19, line 23 claims 30,57	1-50
X	WO 98/21193 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 22 May 1998 (1998-05-22) page 13, paragraph 3 - paragraph 4 page 17; example 1 ----- -/--	1-50



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/61541 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) page 2 page 7, last paragraph page 39, paragraph 2 page 45, paragraph 5 claims 1,5,6	1-50
X	US 6 121 328 A (WEGGLICKI WILLIAM B) 19 September 2000 (2000-09-19)  column 2, line 21 - line 23	1,3,4, 9-14,20, 22-25, 27-32, 37,38, 43,45-50
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A	WO 99/37616 A (AENGGAARD ERIK EMIL ;HAJ YEHIA ABDULLAH IBRAHIM (IL)) 29 July 1999 (1999-07-29) page 3 claims 1-12	1-50
X	MIZUNO K ET AL: "Neuroprotective effect and intraocular penetration of nipradilol, a beta-blocker with nitric oxide donative action" INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, ASSOCIATION FOR RESEARCH IN VISION AND, US, vol. 42, no. 3, March 2001 (2001-03), pages 688-694, XP002956392 ISSN: 0146-0404 page 688, column 1, paragraph 1 page 692, last paragraph - page 693, column 1, paragraph 1 page 688, line 2, paragraph 1 page 691, column 1, paragraph 2  -/--	1-50

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International Application No.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MARTON Z ET AL: "Scavenger effect of experimental and clinically used cardiovascular drugs"</p> <p>JOURNAL OF CARDIOVASCULAR PHARMACOLOGY</p> <p>2001 UNITED STATES,</p> <p>vol. 38, no. 5, 2001, pages 745-753,</p> <p>XP009029273</p> <p>ISSN: 0160-2446</p> <p>page 748, column 2</p> <p>page 752, column 1, paragraph 3</p> <p style="text-align: center;">-----</p>	<p>1,3,4,</p> <p>9-14,20,</p> <p>22-25,</p> <p>27-32,</p> <p>37,43,</p> <p>45-50</p>
X	<p>MOUSA S A ET AL: "MYOCARDIAL ANTI-ISCHEMIC CHARACTERISTICS OF A NOVEL CLASS OF BETA-ADRENOCEPTOR BLOCKERS"</p> <p>INTERNATIONAL JOURNAL OF CLINICAL PHARMACOLOGY THERAPY AND TOXICOLOGY,</p> <p>vol. 30, no. 3, 1992, pages 103-106,</p> <p>XP009029272</p> <p>ISSN: 0174-4879</p> <p>page 104; table 1</p> <p style="text-align: center;">-----</p>	<p>1,3,4,</p> <p>9-14,20,</p> <p>22-25,</p> <p>27-32,</p> <p>37,43,</p> <p>45-50</p>
X	<p>REDDY DOODIPALA SAMBA ET AL: "Comparative antioxidant effects of beta-adrenoceptor blockers, calcium antagonists and U-74500A against iron-dependent lipid peroxidation in murine ventricular microsomal membranes"</p> <p>METHODS AND FINDINGS IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY,</p> <p>vol. 18, no. 9, 1996, pages 559-567,</p> <p>XP009029270</p> <p>ISSN: 0379-0355</p> <p>page 363, column 2; table 1</p> <p style="text-align: center;">-----</p>	<p>1,3,4,</p> <p>9-14,20,</p> <p>22-25,</p> <p>27-32,</p> <p>37,43,</p> <p>45-50</p>
P,X	<p>WO 03/088961 A (YISSUM RES DEV CO ;HAJ-YEHIA ABDULLAH IBRAHIM (IL))</p> <p>30 October 2003 (2003-10-30)</p> <p>page 4 - page 8</p> <p>page 57</p> <p>claims 1-9</p> <p style="text-align: center;">-----</p>	<p>1-50</p>

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IL 03/00986

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13, 22-36, 45-50 (all in part); 14, 15, 37, 38

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-13, 22-36, 45-50 (all in part); 14, 15, 37, 38

Use of compounds comprising a beta blocker component derived from a commercially available beta blocker as defined in claim 14, a ROS scavenger component and optionally a NO donor component for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11.

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2. claims: 1-13, 18, 19, 21-36, 41, 42, 44-50 (all in part); 16,  
39

Use of compounds according to formula I as defined in claim 16, formula IIIA and IVA as defined in claim 18 and compounds 14, 15, 20, 21, 26-35 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11.

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3. claims: 1-13, 19-36, 41, 42, 44-50 (all in part); 17, 40

Use of compounds according to formula II as defined in claim 17 and compounds 22-25 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11.

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4. claims: 1-13, 18-36, 41-50 (all in part);

Use of compounds according to formula IA as defined in claim 18 (compounds as defined in claims 14 or 15 being excluded) and compounds 1, 2, 7-24 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11.

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5. claims: 1-13, 18, 19, 21-36, 41, 42, 44-50 (all in part);

Use of compounds according to formula IIA as defined in claim 18 (not being included within formula I and II) and compounds 37, 42, 47, 52, 67, 72, as defined in claim 20 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11.

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6. claims: 1-13, 18, 19, 21-36, 41, 42, 44-50 (all in part);

Use of compounds according to formula VA as defined in claim 18 (not being included within formula I and II) and compounds 39, 40, 44, 45, 49, 50, 54, 55, 69, 70, 74, 75 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. claims: 1-13, 20-36, 43-50 (all in part);

Use of compounds 36, 41, 46, 51, 66, 71 and 38, 43, 48, 53, 68, 73 as defined in claim 21 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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